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Peter Huszthy, Jerald S. Bradshaw, and Reed M. Izatt

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Department of Chemistry  
Brigham Young University  
Provo, UT 84602-46728. PERFORMING ORGANIZATION  
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A chiral dimethylpyridino-18-crown-6 ligand was attached to silica gel by first forming an allyloxy-substituted crown. This material was treated with triethoxysilane and then coated and covalently attached to silica gel. This report shows the synthesis of the silica gel-bound chiral crown and its use in separating  $\alpha$ -(1-naphthyl)ethylammonium perchlorate into its (R)- and (S)-forms.

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Enantiomeric Separation of Chiral Organic Ammonium  
Salts by Chiral Pyridino-18-crown-6 Ligands

by

Peter Huszthy, Jerald S. Bradshaw, and Reed M. Izatt

Department of Chemistry  
Brigham Young University  
Provo, UT 84602-4672

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The design, synthesis and use of macrocycles capable of selective recognition of other molecules is of great interest to workers in many fields.<sup>1-3</sup> Our interest is in the area of enantiomeric recognition and has focused on the interactions of chiral crown macrocycles with chiral organic ammonium cations.<sup>4-10</sup> We have chosen interactions of the chiral pyridino-18-crown-6 ligands because they form relatively strong complexes with the organic ammonium salts<sup>11</sup> and they can be prepared in the laboratory with various substituents on chiral positions on the macroring. We have made a systematic study of how the extent of enantiomeric recognition varies with crown substituent, guest type and solvent.<sup>6,7,10</sup>

We have now covalently attached chiral dimethylpyridino-18-crown-6 onto silica gel. More than a decade ago, Cram and coworkers covalently attached a different chiral crown ether to silica gel using another method, and they used this system for separation of the enantiomers of chiral organic ammonium salts.<sup>11</sup> This report describes the synthesis of chiral dimethyl-4-allyloxy-18-crown-6 (1) (an analogue that can be bonded to silica gel) (see Scheme II) and its attachment to silica gel. A preliminary study of the separation of the (*R*)- and (*S*)-forms of NapEtClO<sub>4</sub> using the new silica gel-bound chiral crown (Scheme II) is also reported.

4-Allyloxy-2,6-pyridinedimethyl ditosylate, needed for the synthesis of the chiral crown (1) that is capable of being attached to silica gel, was prepared as shown in Scheme I. We have found that the use of powdered KOH in THF is a superior base-solvent system for the preparation of tosylates from alcohols and tosyl chloride.<sup>6,7,10</sup>

New chiral macrocycle (*S,S*)-1 was prepared as shown in Scheme II. The

synthesis of silica gel-bound chiral dimethyl-substituted pyridino-18-crown-6 [(*S,S*)-9] is also shown in Scheme II. Starting (*S,S*)-dimethyltetraethylene glycol [(*S,S*)-7] was prepared as reported.<sup>12,13</sup> The attachment of (*S,S*)-1 to silica gel was accomplished by first forming the chiral crown-triethoxysilane by a simple hydrosilylation reaction and heating this material in toluene in the presence of silica gel.<sup>14-16</sup> The silica gel contained about 0.25 mmol of chiral crown per gram as determined by a combustion analysis.

A preliminary study on the separation of (*R*)- and (*S*)-NapEtClO<sub>4</sub> using silica gel-bound chiral crown 9 is shown in Figure 1. Racemic NapEtClO<sub>4</sub> was placed on a column containing (*S,S*)-9. The elution solvent was a mixture of 70% acetone and 30% CH<sub>3</sub>OH by volume. We used acetone because, initially, we observed a high enantiomeric selectivity in pure acetone. This selectivity proved to be an artifact of the reaction of the ammonium salt with acetone to form a Schiff-base. The relative amounts of (*R*)- and (*S*)-NapEtClO<sub>4</sub> in each sample were determined from the HPLC chromatogram of the corresponding acetamide derivatives. Each fraction was treated with base and acetic anhydride. Blank determinations using known mixtures of the (*R*) and (*S*) salts and phthalimide as internal standard showed that this technique gave quantitative values for the amounts of the chiral salts in the sample.

As can be seen in Figure 1, (*S,S*)-9 does separate the (*R*)- and (*S*)-forms of NapEtClO<sub>4</sub>. As expected, the (*S*)-form passes through the column first although it is contaminated by some of the (*R*)-form. (*S,S*)-9 interacts more strongly with (*R*)-NapEtClO<sub>4</sub> so that the (*R*)-form should come off the column last. This is a preliminary

experiment. This separation and that of other chiral organic ammonium salts need to be studied in greater detail. The incomplete separation of (*S*)-NapEtClO<sub>4</sub> could be caused by overloading the column or the use of the wrong solvent system.

It is possible that attachment to silica gel through the pyridine ring would put the steric portion of the chiral crown too close to the solid support. This could reduce the host-guest interaction and could change the degree of enantiomeric recognition. Indeed, Schomburg and co-workers found that the chiral phase needed to be more than three atoms removed from the solid support for effective enantiomeric separation in supercritical fluid chromatography.<sup>17</sup> Preliminary results using (*S,S*)-**9** shown in Figure 1, indicate that there is recognition in this system. In the future, a chiral pyridino-crown similar to **9** but with a long chain spacer will be prepared, attached to silica gel, and tested.

### Experimental Section

The <sup>1</sup>H NMR spectra were obtained at 200 MHz in CDCl<sub>3</sub> with TMS as the internal standard unless otherwise indicated. Melting points are uncorrected. Starting materials were used as purchased from Aldrich Chemical Company unless otherwise noted. Dimethyl 4-allyloxy-2,6-pyridinedicarboxylate (**4**),<sup>18</sup> 4-allyloxy-2,6-pyridinedimethanol (**5**)<sup>18</sup> and chiral dimethyl-substituted tetraethylene glycol (*S,S*-**7**)<sup>12,13</sup> were prepared as reported. Chelidamic acid monohydrate (**2**) was made from chelidonic acid and concentrated NH<sub>4</sub>OH as reported.<sup>19</sup>

**Dimethyl Chelidamate (3)** (Scheme I). Thionyl chloride (144 mL, 235 g,

2.0 mol) was slowly added to a stirred mixture of 71.8 g (0.36 mol) of **2** and 720 mL of CH<sub>3</sub>OH in an ice-salt bath. The mixture was stirred in an ice-salt bath for 1 h and at rt for 2 days. The solvent was evaporated and the residue was mixed well with 750 mL of an 8% (w/v) NH<sub>4</sub>O<sub>2</sub>CCH<sub>3</sub> solution and stored in a refrigerator for 2 days. The white crystals were filtered, washed 3 times with 100-mL portions of cold water and dried. After recrystallization from CH<sub>3</sub>OH, 66 g (88%) of pure **3** was obtained; mp 170-171 °C (lit.<sup>20</sup> mp 169-169.5 °C).

**4-Allyloxy-2,6-pyridinedimethyl Ditosylate (6)** (Scheme I). To a stirred suspension of 12.6 g (0.201 mol, 87.5%) of well powdered KOH in 45 mL of THF was added 8.8 g (0.045 mol) of **5**<sup>18</sup> dissolved in 120 mL of THF. After 10 min of stirring at 0 °C under Ar, 22.9 g (0.12 mol) of tosyl chloride dissolved in 120 mL of THF was added dropwise. After stirring the reaction mixture at 0 °C for 2 h and at rt for 4 h, the solvent was evaporated under reduced pressure. The residue was dissolved in a mixture of 1200 mL of CH<sub>2</sub>Cl<sub>2</sub>, 200 g of ice and 400 mL of water. The phases were mixed well and separated. The organic phase was dried (MgSO<sub>4</sub>), filtered and the solvent was removed under reduced pressure to give 25.6 g of crude product. The product was recrystallized from a ClCH<sub>2</sub>CH<sub>2</sub>Cl-CH<sub>3</sub>OH mixture to give 19.6 g (86%) of **6**; mp 79-81 °C; IR (KBr) 1386, 1177 cm<sup>-1</sup>, <sup>1</sup>H NMR δ 2.44 (s, 6 H), 4.50-4.58 (m, 2 H), 4.98 (s, 4 H), 5.29-5.48 (m, 2 H), 5.88-6.10 (m, 1 H), 6.82 (s, 2 H), 7.33 (d, 4 H, J = 10 Hz), 7.80 (d, 4 H, J = 10 Hz). Anal. Calcd. for C<sub>24</sub>H<sub>25</sub>NO<sub>7</sub>S<sub>2</sub> : C, 57.24; H, 5.00. Found: C, 57.41; H, 5.12.

**19-Allyloxy-(4*S*,14*S*)-(+)-4,14-dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo [15.3.1] heneicosa-1(21),17,19-triene (1)** (Scheme II). To a well stirred suspension of 2.0 g (66 mmol) of NaH (80% dispersion in mineral oil) in 40 mL of pure and dry THF at 0 °C under Ar was added dropwise 5.23 g (23.5 mmol) of (*S,S*)-7 dissolved in 220 mL of THF. The mixture was stirred at 0 °C for 10 min, at rt for 30 min and at reflux temperature for 3 h. The reaction mixture was cooled to -10 °C and 12.5 g (24.8 mmol) of 6 dissolved in 260 mL of THF was added dropwise. The resulting mixture was stirred at -10 °C for 20 min and then at rt for 36 h. After the reaction was complete, the solvent was evaporated under reduced pressure. The residue was dissolved in a mixture of 1000 mL of CH<sub>2</sub>Cl<sub>2</sub>, 100 g of ice and 200 mL of water. The resulting mixture was mixed well and separated. The aqueous phase was shaken twice with 200-mL portions of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phase was dried (MgSO<sub>4</sub>), filtered and the solvent was removed under reduced pressure. The residue was purified on neutral alumina using toluene then C<sub>2</sub>H<sub>5</sub>OH/toluene (1/80) as eluents to give 5.42 g (60%) of 1 as a colorless oil;  $[\alpha]_D^{22} + 26.88^\circ$  (*c* = 1.40, CHCl<sub>3</sub>); IR (neat) 3082, 1598, 1575, 1454, 1360, 1110, 1042 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  1.12 (d, 6 H, *J* = 7 Hz), 3.33-3.67 (m, 12 H), 3.68-3.87 (m, 2 H), 4.51-4.61 (m, 2 H), 4.72 (s, 4 H), 5.22-5.45 (m, 2 H), 5.88-6.11 (m, 1 H), 6.76 (s, 2 H); MS (low voltage), *m/e* 381 (*M*<sup>+</sup>). Anal. Calcd. for C<sub>20</sub>H<sub>31</sub>NO<sub>6</sub> : C, 62.97; H, 8.19. Found: C, 62.88; H, 7.92.

**Silica Gel-bound Chiral Crown 9** (Scheme II). A mixture of 1.06 g (2.78 mmol) of 1 and 0.77 mL (0.685 g, 4.1 mmol) of triethoxysilane (freshly distilled under Ar) was stirred vigorously in a 5-mL one-necked flask equipped with a rubber septum. Two drops of PC072 catalyst (hüls America, Inc.) was added through the rubber

septum. The hydrosilylation reaction was carried out as reported by Lewis.<sup>30</sup> After stirring the mixture for 6 days at rt, the <sup>1</sup>H NMR spectra showed that the olefin protons had disappeared. The volatile compounds were removed from the reaction mixture under vacuum (0.02 mm) and the residue (1.49 g, 98%) was stirred with 6.0 g of silica gel (Davison Chemical, pore diameter 150 Å, 60-200 mesh) in 100 mL of toluene at 90 °C for 2 days. After the reaction was completed, the silica gel was filtered and washed with toluene/methanol (1/1) and then with methanol. The filtrate was evaporated to give 0.47 g of unreacted organic material. This means that about 1.0 g (1.8 mmol) of crown was attached to the silica gel. The silica gel containing the crown was dried in a vacuum oven at 70 °C for 5 h. A sample of blank silica gel was dried the same way and it gave a combustion analysis of 0% C and 0.35% H. The combustion analysis of **9** gave C, 5.83; H, 1.16. This indicates that each gram of **9** contained 0.243 mmol (by %C) or 0.251 mmol (by %H) of the chiral crown.

**Separation of the *R*-(+) and *S*-(-) Isomers of NapEtClO<sub>4</sub> Using (S,S)-**9**.** The preparation of (*R*)-(+)- and (*S*)-(-)-NapEtClO<sub>4</sub> was described earlier.<sup>4</sup> Pure (*R*)- and (*S*)-NapEtClO<sub>4</sub> were obtained by recrystallization from butyl acetate; (*R*)-NapEtClO<sub>4</sub>; mp 184-185 °C, [ $\alpha$ ]<sub>365</sub><sup>22</sup> + 21.27° (c = 1, C<sub>2</sub>H<sub>5</sub>OH); (*S*)-NapEtClO<sub>4</sub>; 183-184 °C; [ $\alpha$ ]<sub>365</sub><sup>22</sup> - 21.12° (c = 1, C<sub>2</sub>H<sub>5</sub>OH). (*R*)-NapEtClO<sub>4</sub> (40.0 mg) and 40.0 mg of (*S*)-NapEtClO<sub>4</sub> were dissolved in 8.0 mL of THF. (C<sub>2</sub>H<sub>5</sub>)<sub>3</sub>N (50 µL) was added to 2.0 mL of this solution and then 15 µL of acetic anhydride was added and the mixture was stirred at rt for 10 min. TLC analysis (silica gel with CH<sub>3</sub>CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>/hexane (6/4) as eluant) showed that a complete conversion of the perchlorate salt into the N-acetyl derivative



of  $\alpha$ -(1-naphthyl)ethylamine had occurred. After evaporation of the solvent under reduced pressure, the residue was dissolved in a mixture of 20 mL of  $\text{CH}_3\text{CO}_2\text{C}_2\text{H}_5$  and 20 mL of  $\text{H}_2\text{O}$ . The mixture was shaken well and separated. The organic phase was dried ( $\text{MgSO}_4$ ), filtered and the solvent was evaporated to give 15.7 mg (100%) of N-[ $\alpha$ -(1-naphthyl)ethyl]acetamide as white crystals; mp 158-159 °C;  $^1\text{H}$  NMR  $\delta$  1.63 (d, 3 H,  $J = 6$  Hz), 1.92 (s, 3 H), 5.80-6.00 (m, 2 H), 7.35-8.15 (m, 7 H); IR (KBr) 3292, 1631, 1540, 1372, 1274, 1125, 965, 780, 609  $\text{cm}^{-1}$ . The enantiomeric ratio was determined to be 50.24% (*R*) and 49.76% (*S*) by HPLC analysis on a chiral column as mentioned below. The remainder of the above THF solution (6.0 mL) was evaporated to give 60.0 mg of racemic NapEtClO<sub>4</sub> which was dissolved in 1.0 mL of a  $\text{CH}_3\text{OH}$ /acetone (3/7) mixture and was placed onto the top of a column of 4.22 g of (*S,S*)-**33** and eluted with the  $\text{CH}_3\text{OH}$ /acetone (3/7) mixture. The flow rate of the eluant was 0.088 mL/min. The amount of NapEtClO<sub>4</sub> salt in each 4-mL fraction was determined using the N-acetyl derivatization described above. The determination was performed on Hewlett Packard HP 1090 Liquid Chromatograph (Maximum pressure 300 ppsi, flow rate = 1 mL/min) using a Chiralcel OB chiral column (Daicel Chemical Industries, Ltd.). The internal standard was phthalimide. The HPLC solvent was 20% 2-propanol/ 80% n-hexane. The amount in milligrams of (*R*)( $m_R$ )- and (*S*)-NapEtClO<sub>4</sub>( $m_S$ ) in each fraction was determined from peak areas as calibrated from known samples. The calculated concentrations of (*R*)- and (*S*)-NapEtClO<sub>4</sub> were plotted versus the mL of eluant as shown in the smooth curve in Figure 1.

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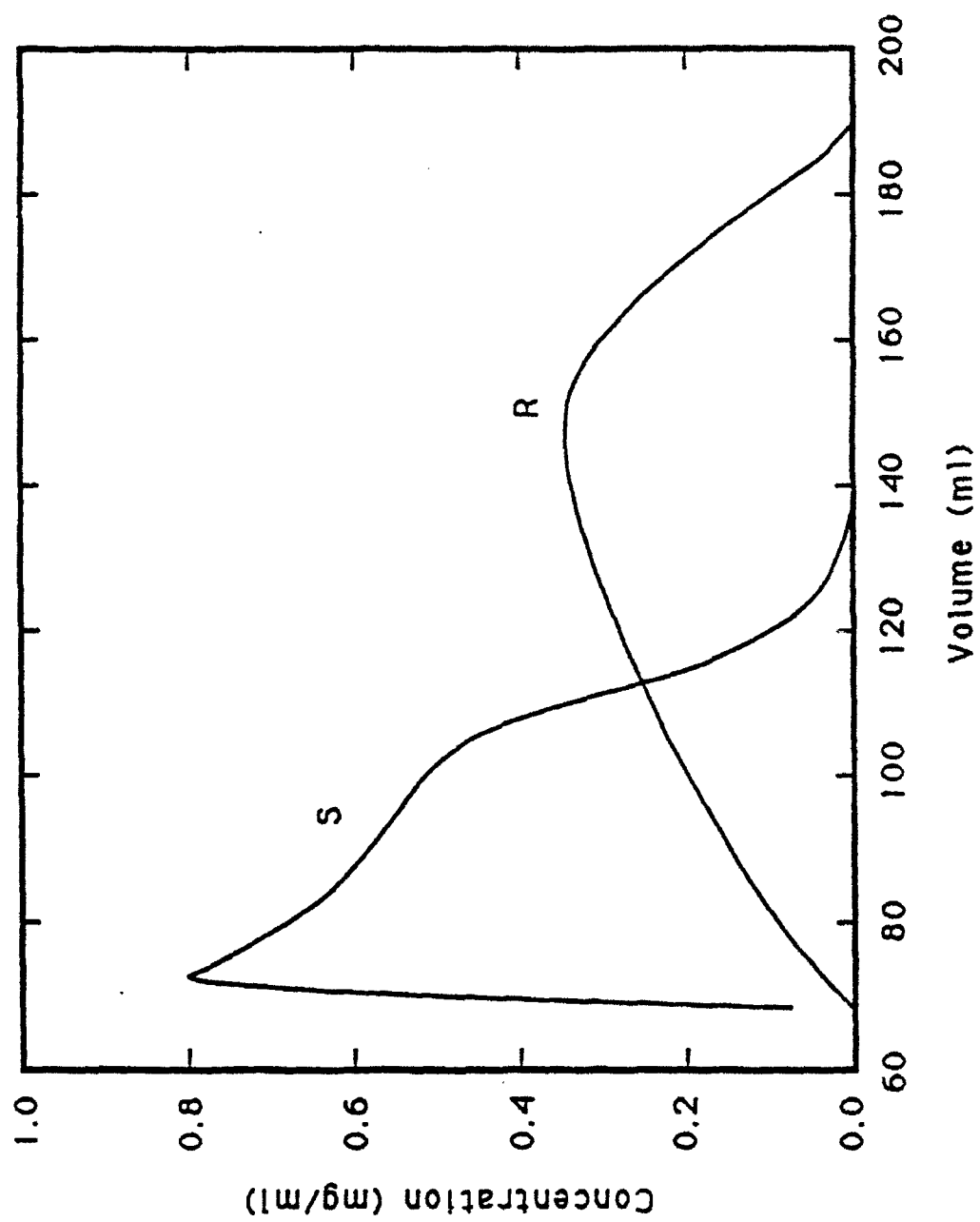
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## FIGURES AND SCHEME CAPTIONS

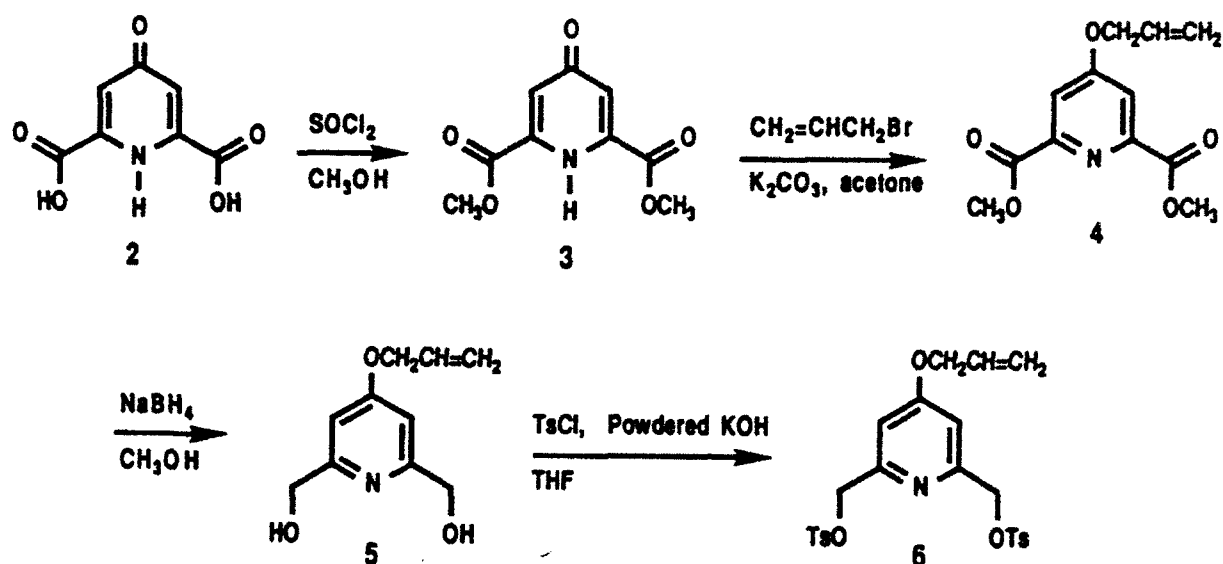
Figure 1. A Smooth Curve Showing the Separation of the Enantiomers of (*R*)- and (*S*)-NapEtClO<sub>4</sub> on (*S,S*)-**9** using Acetone/CH<sub>3</sub>OH (7/3) as Eluant.

Scheme I. Preparation of 4-Allyloxy-2,6-pyridinedimethyl Ditosylate (**6**).

Scheme II. Preparation of Chiral Allyloxypyridino Crown **1** and Silica Gel-bound Chiral Crown **9**.



## Scheme I. Preparation of 4-Allyloxy-2,6-pyridinedimethyl Ditosylate (6)



## Scheme II. Preparation of Chiral Allyloxypyridino Crown 1 and Its Attachment to Silica Gel

